Viral Hemorrhagic Fevers Summary

Introduction

The viral hemorrhagic fevers (VHF's) are a group of clinical febrile illnesses with a propensity to cause significant bleeding. These illnesses are caused by a group of RNA viruses which belong to four distinct viral families: Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae. The two viruses considered to be the greatest bioterrorism threats are **Ebola** and **Marburg**, the two members of the **filovirus** family, which are categorized as category A bioweapon agents. These viruses characteristically cause high mortality and morbidity, are person to person spread, are highly infectious at a low dose by the aerosol route, are stable in the environment, and large-scale production is feasible. Other viruses which could conceivably be used as terrorist weapons, but not considered as great a threat as the filoviruses, include:

> **Arenaviruses:** Lassa Fever (Africa) and the New World Hemorrhagic Fevers - Bolivian Hemorrhagic Fever (BHF, Machupo virus), Argentine Hemorrhagic Fever (AHF, Junin virus), Venezuelan Hemorrhagic Fever (Guanarito virus), and Brazilian Hemorrhagic Fever (Sabia virus)
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> **Bunyaviruses:** Crimean-Congo Hemorrhagic Fever (CCHF), Rift Valley Fever (RVF)
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> **Flaviviruses:** Dengue, Yellow Fever, Omsk Hemorrhagic Fever, and Kyasanur Forest disease

State biological weapons programs have shown interest in hemorrhagic fever viruses (HFV's) as weapons; the former Soviet Union weaponized significant quantities of Marburg, Ebola, Lassa, Junin, and Machupo. The Aum Shinrikyo cult in Japan attempted to gain access to Ebola during the Kikwit, Zaire Ebola outbreak in the mid-90's.

Natural outbreaks of disease from these viruses have demonstrated their potential as deadly weapons and their ability to spread from person to person in some cases. The reservoir of several of the HFV's is either rodents or insects (ticks or mosquitoes); the reservoir(s) of Ebola and Marburg are unknown. In natural outbreaks of Ebola and Marburg, contact precautions have been sufficient to interrupt person-to-person spread. Airborne precautions have not been necessary, although some animal studies have raised concern about spread via small-particle aerosols.

Clinical Features

Clinical manifestations of VHF's vary according to the specific etiologic virus and may overlap, making specific clinical diagnosis unlikely. The incubation period varies from 2 to 21 days, and may be inoculum dependent. Prodromal symptoms are typical, with several days of fever, myalgias, headache, malaise, arthralgias, nausea, diarrhea, and

abdominal pain. With some VHF's, such as CCHF, abdominal pain may be pronounced, mimicking an acute abdomen. All VHF's are characterized by an abrupt onset of symptoms, with the exception of the arenaviruses, where onset is more insidious.

After the prodrome, patients may develop conjunctivitis and pharyngitis, and most VHF patients have a rash, with the dermal manifestations varying by etiology. As these diseases progress, patients may exhibit a progressively worsening bleeding diathesis, with petechiae, conjunctival and mucosal hemorrhage, hematuria, hematemesis, and melena, followed by DIC and hypotension. As the patient worsens, CNS signs ensue, including delirium, seizures, and coma. Shock and multiple organ system failure presage death. Case fatality rates vary according to the viral etiology, ranging from less than 5 percent to approximately 70 to 90 percent with Ebola Zaire subtype.

Evacuation for ICU care during the incubation period is acceptable; after onset of symptoms it is not advisable.

Epidemiologic Indicators: With natural cases, historical risk factors such as travel to Africa, Asia, or South America, or exposure to other patients may be present. In nature, most of these infections are spread by nosocomial or close personal contact with other victims, or by exposure to insect vectors. In a bioterrorism attack, patients may have common geographic factors, which may indicate simultaneous (aerosol) exposure. Presence of these viruses outside their normal range, and high attack and mortality rates may indicate non-natural exposure.

Diagnosis and Treatment

Presenting Symptoms (Clinical Diagnosis)

- Fever
- Malaise
- Erythematous Rash or Flushing (early)
- Conjunctivitis
- Pharyngitis
- Myalgias
- Abdominal Pain
- Nausea and/or Diarrhea
- Petechiae and Hemorrhagic Rash/Purpura (late)
- Hematemeis, Hemoptysis, Epistaxis, Hematochezia, or Melena
- Hypotension
- Signs of CNS Dysfunction: Seizures, Delirium, Coma

Laboratory Clinical Diagnostic Testing (Blood, Urine): WBC with Differential, Platelet Count, PT/PTT and Bleeding Time, LFT's, Fibrin Split Products, Fibrinogen, UA and BUN/Creatinine, Electrolytes, Glucose, and pH and bicarbonate levels (acid/base status).

Specific Diagnostic Testing (only available at specialized laboratories): Antigen-Capture ELISA, RT-PCR (most useful clinically), IgM by Antibody-Capture ELISA, Viral isolation (requires BSL-4 laboratory – CDC or USAMRIID), acute and convalescent IgG serologies in survivors (only helpful retrospectively)

Differential Diagnosis: Viral Hepatitis, Gram-negative sepsis, Toxic Shock Syndrome, Meningococcemia, other bacterial sepsis, Rocky Mountain Spotted Fever or other rickettsial disease, leptospirosis, borreliosis, Dengue Hemorrhagic Fever (DHF), malaria, septicemic plague, hemorrhagic smallpox.

Isolation: Strict VHF-specific barrier precautions initiated on **suspicion** of VHF disease. See guidelines in JAMA 2002, May 8: 287; 2391-2405, or at the CDC bioterrorism web site:

http://www.bt.cdc.gov/agent/vhf/index.asp

Also airborne precautions and a negative-pressure isolation room are recommended, if such a room is available. Close medical surveillance for all those with close or high-risk contact or blood exposure within 21 days of a patient's onset of symptoms. Convalescent patients should refrain from sexual activity for 3 months (filoviral or arenaviral infections).

Decontamination: Environmental surfaces and contaminated equipment – 1:10 to 1:100 dilution of household bleach (hypochlorite) or other EPA-registered disinfectant. Linens should be handled per CDC guidelines.

Treatment:

Intensive Supportive Care

Intravenous IND Ribavirin therapy (available from CDC or USAMRIID) – recommended for VHF of unknown etiology while diagnostic confirmation is pending VHF known to be due to Arenaviruses or Bunyaviruses (Ribavirin has efficacy against Lassa Fever, some new world Arenaviruses such as AHF, CCHF, RVF, and HFRS). See guidelines for dosing in JAMA 2002 May 8; 287:2391-2405 or at web link: http://jama.ama-assn.org/issues/v287n18/ffull/jst20006.html The main side effect is a reversible hemolytic anemia. Ribavirin has no efficacy against Filoviruses or Flaviviruses, and is contraindicated in pregnancy.

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Case Scenarios – Viral Hemorrhagic Fever
For CE Modules – Emergency Physician

Case 1 - Emergency Physician

You are the on-duty staff emergency physician in a major academic teaching hospital. A young medical resident from your hospital calls at midnight from the Ivory Coast in Africa. While doing missionary work at a small local hospital in that country, he is caring for a group of patients who have recently exhibited a febrile illness with a severe bleeding diathesis, and two have died. Healthcare providers have been using full barrier precautions with eye and respiratory protection because of a history of ebola infection in the past in this region. Yesterday they received word from the CDC that ebola had been confirmed. Today while cutting off tape covering the sleeves of his gown and his gloves, the young doctor accidentally pierced the skin of his wrist with a pair of bandage scissors. There was blood on the outside of the gown sleeve, and minimal blood at the site of the wound. He asks you for advice on what he should do. Though small, the local hospital where he is working has modern ICU capabilities with unused beds and sufficient staff.

You correctly advise him to:

A) Remain in place for 21 days under close medical observation for evidence of VHF symtomatology.
B) Begin post-exposure prophylaxis with oral ribavirin immediately
C) Arrange for immediate transport within 48 hours to the closest major medical center in Europe with isolation and intensive care capabilities.
D) Wait to see if symptoms occur, and then arrange transport out of the area.
E) Either A or C are correct.

(Answer: E)

Case 2 – Emergency Physician

You are the on-duty staff emergency physician at a community hospital in Atlanta on a Sunday morning, and the Emergency Department is unusually quiet. A 35 year-old female technician who works in the high containment laboratory at CDC presents to your facility complaining of fever, malaise, erythematous rash, conjunctivitis, and myalgias. This morning she had a bought of epistaxis and had difficulty stopping the bleeding with local pressure. Last weekend at CDC she was working with blood specimens from an outbreak of febrile hemorrhagic disease in agricultural workers in Argentina, and she accidentally stuck herself with a contaminated needle through her glove while attempting to recap a syringe. She was afraid to tell her supervisor at CDC for fear she would be disciplined for breaking safety procedures. Her symptoms began yesterday (Saturday). Appropriate actions for you to take with this patient include:

A) Immediate isolation in the Emergency Department and hospitalization in a negative pressure isolation room with strict barrier and airborne precautions for those caring for her, including ED personnel prior to her transfer.
B) Immediate institution of IV Ribavirin therapy after obtaining the patient's informed consent
C) Notify the local health department and CDC of this suspected case of VHF, and ask for CDC advice on management
D) Consider air evacuation to the BSL-4 isolation unit at USAMRIID at Fort Detrick, Maryland.
E) All except D are correct.

Case 3 – Hospital Infection Control Practitioner

You are the hospital infection control nurse at the hospital where Case 2 is being admitted. You receive a phone call from the chief nurse of the ICU where the patient is being admitted. There is concern among the nursing staff about the possibility of nosocomial infection. Measures you advise include:

A) Limiting the numbers of nursing staff caring for this patient and restricting access to the patient for nonessential staff and visitors
B) Double gloves, impermeable gowns, leg and shoe coverings
C) Face shields and eye protection
D) Respiratory protection (airborne precautions)
E) All of the above

(Answer - E)